Remarks

A. *Status of the Claims*

Claims 67-68, 73, 100-102, 104-107, 110, 116-120, and 125 were pending at the time of the Action. Claim 101 has been amended to independent form. Claims 105-107 have been amended to depend from claim 101. New claims 135 and 136 have been added. Claims 67-68, 73, 100, 102, 104, 110, 116-120, and 125 have been canceled. Applicants reserve the right to pursue the subject matter of any of the canceled claims in one or more continuing applications. Claims 101, 105-107, and 135-136 are now pending.

B. *The Claims are Enabled*

The Action rejects claims 67-68, 73, 100-102, 104-107, 110, 116-120, and 125 under 35 U.S.C. § 112, first paragraph, for lack of enablement. Applicants traverse this rejection.

1. Analysis of the *Wands* Factors

An analysis of the *Wands* factors demonstrates that a person of ordinary skill in the art could make and use the claimed invention without undue experimentation. Furthermore, Applicants have provided the Neu and Schuster Declarations to demonstrate that the claimed method works. Declarations provided after the filing date to show that the claimed invention works must be considered by the Examiner. *See* MPEP § 2164.05.

a) The Breadth of the Claims and the Nature of the Invention

The current claims are directed to a method of treating acute respiratory distress syndrome in a mammal comprising administering a mammalian ACE2 polypeptide to the mammal, wherein the acute respiratory distress syndrome is treated.

b) The State of the Art and the Level of Ordinary Skill in the Art

The use of protein therapy in the treatment of diseases is well-known in the medical field (Neu Declaration, para. 6). Examples of such protein therapies are described in the publication *Scientific Considerations Related to Developing Follow-On Protein Products*, 2004, which is cited in the Action at page 9. This publication mentions such drugs as Epogen®, which is a ***protein therapy*** based on human erythropoietin; and Neupogen®, which is a ***protein therapy*** based on granulocyte colony-stimulating factor. As pointed out in the Action, *Scientific Considerations Related to Developing Follow-On Protein Products* also notes that ***six*** companies manufacture ***FDA-approved*** versions of human growth hormone (paragraph bridging pages 5-6). Thus, protein therapy was well-known and commercially successful in the art and the level of skill was high.

Much of the Examiner's alleged evidence of unpredictability is not relevant to the current claims. For example, the Examiner repeatedly raises arguments based on the unpredictability of ***expressing*** proteins at the target site (*see e.g.,* Action, pages 4-6). The claims, however, recite administering an ACE2 ***polypeptide***. Thus, there is not requirement for the protein to be expressed in the mammal being treated.

As a further example, the Action's arguments about the unpredictability of getting the protein into cells is based on generalizations or mischaracterizations of protein therapy that fail to consider that the active ACE2 protein is ***secreted***. As a secreted protein, ACE2 is effective in circulation. Thus, someone of ordinary skill in the art would understand that the ACE2 polypeptide could be administered according to the teachings on at least pages 21-22 of the specification. Furthermore, the Neu and Schuster Declarations demonstrate that an effective amount of ACE2 polypeptide can be delivered by intravenous injection or intraperitoneal injection, two routes of administration disclosed on page 21 of the specification.

The Examiner also undertakes a lengthy discussion of the unpredictability of using liposomes as delivery vehicles (Action, p. 8-9). It is unclear what aspect of the claims the Examiner believes this is relevant to.

In the paragraph bridging pages 6-7 in the Action, the Examiner states that deletion of an individual gene in a knockout animal may prove so drastic or so widespread as to create an amalgam of phenotypes whose interpretation becomes confounded by the interaction of various new physiologic changes. The Examiner, therefore, questions the interpretation of the phenotypes observed in the ACE2 knockout mouse reported in the specification. However, the inventors validated the phenotype of the ACE2 knockout mouse by creating an ACE/ACE2 double-knockout mouse, which is also described in the specification. In the ACE/ACE2 double-knockout mice, it was shown that ablation of ACE expression on an ACE2 deficient background ***abolished*** the heart failure phenotype of ACE2 single-knockout mice (specification p. 29, first paragraph and p. 38, last paragraph). ***This shows that only the expected ACE2 activity on the polypeptides of the RAS systems (angiotensin I and angiotensin II conversion) was observed in the animal model.*** This refutes the Examiner's assertion, which is based on generalizations from other animal models.

The Examiner also cites Acton *et al.* (US 6,632,830) as providing a contradictory teaching as to the function of ACE2. As discussed in the specification and in previous responses, Acton ***incorrectly predicted*** a function for ACE2 based on its homology to ACE. No actual studies of ACE2 function were reported by Acton. ***Acton's prediction was proven wrong*** by actual studies disclosed in the present specification. The error in Acton has been confirmed by at least Imai *et al.*, the Neu Declaration, and the Schuster Declaration. The Examiner's continued reliance on a reference that he knows to be factually inaccurate is improper.

Finally, many of the Examiner's concerns are directed to safety issues (*e.g.*, undesirable immune responses). However, testing for the full safety and effectiveness of a particular drug for human use is more properly left to the FDA. *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995). There is nothing in the patent statute or any other statutes that gives the Patent Office the right or the duty to require an applicant to prove that compounds he is claiming, and which he has stated are useful for "pharmaceutical applications," are safe, effective, and reliable for use with humans. *In re Krimmel*, 292 F.2d 948, 954 (C.C.P.A. 1961); *see also* MPEP § 2164.01(c).

c) The Guidance Provided by the Specification

The present specification provides sufficient guidance to enable a person of ordinary skill in the art to make and use the claimed invention without undue experimentation. This is further supported by the studies described in the Neu and Schuster Declarations, which provide evidence that, ***by following the teachings in the specification***, someone skilled in the art can make and use the claimed invention without undue experimentation. Such declarations must be considered by the Examiner in evaluating enablement. *See* MPEP § 2164.05.

The present specification provides a new paradigm for the regulation of the renin-angiotensin system. The present specification discloses that hypertension, as well as other cardiac, lung, and kidney diseases are associated with an ACE2 decreased state (*see e.g.*, p. 2, ln. 28 to p. 3, ln. 6). In particular, the rat and mouse studies in the present specification demonstrate that an ACE2 decreased state is associated with cardiovascular, renal, and lung diseases. For example, studies on the ACE2 knockout mouse demonstrated that loss of ACE2 leads to increases the susceptibility of the lungs to injury (p. 40, ln. 12-20).

The specification further showed in the ACE/ACE2 double knockout mice, that ablation of ACE expression on an ACE2 deficient background ***abolished*** the heart failure phenotype of ACE2 single knockout mice (specification p. 29, first paragraph and p. 38, last paragraph). This

shows that ***only*** the expected ACE2 activity on the polypeptides of the RAS systems (angiotensin I and angiotensin II conversion) was observed in the animal model. This refutes the Action's assertion that the interpretation of the results from this animal model could have been confounded by an amalgam of phenotypes and/or compensatory systems (Action, p. 6-7).

Furthermore, the evolutionary conservation of ACE2 structure and activity among mammals, as well as other organisms, is further evidence that the currently claimed method could be practiced in any mammal (*see e.g.,* Specification, FIGs. 1A, showing an alignment of the amino acid sequences of ACE2 from human, rat, and mouse, which illustrates the identities and similarities between these sequences). In addition, results in flies showed that a P-element mutation associated with the ACE homologue, ACER, results in a severe and lethal defect of heart morphogenesis providing further evidence that ACE/ACE2 functions in the heart have been conserved through evolution (Specification, p. 30, ln. 28 to p. 31, ln. 2). The previously cited publication entitled "Structure, Evolutionary Conservation, and Function of Angiotensin- and Endothelin-Converting Enzymes" (Macours *et al.*, *International Review of Cytology*, 239:47-97 (2004)), is further evidence of the conservation of the ACE/ACE2 system.

In addition, the specification discloses that AngI and AngII are substrates for ACE2, which functions as a carboxypeptidase to cleave a single residue from each of AngI and AngII (p. 2, ln. 5-10). Applicants also provided previously the results of a BLAST search of the ACE2 substrate, AngII, which shows that AngII is present in numerous mammals including *Pan troglodytes, Mus musculus, Homo sapiens, Callithrix jacchus, Gorilla gorilla, Canis familiearis, Macaca mulatta, Rattus norvegicus, Ovis ammon,* and *Pongo pygmaeus*. In view of the evidence that ACE2 structure and function is conserved among mammals, one would expect that the currently claimed method could be practiced in any mammal (*see* Neu Declaration, para. 5).

Accordingly, those of ordinary skilled in the art would have appreciated the therapeutic benefit of a method of treating acute respiratory distress syndrome in a mammal comprising administering a mammalian ACE2 polypeptide to the mammal.

d) The Neu Declaration

As discussed in the previously submitted declaration of Dr. Nikolaus Neu ("Neu Declaration"), Imai *et al.* (*Nature*, 436:112-116 (2005); IDS reference C61)) is further evidence that those of skill in the art can make and use the claimed invention without undue experimentation (*see* Neu Declaration, para. 7). Imai *et al.* demonstrated that injecting ACE2 knockout mice or acid-treated wild-type mice with a recombinant human ACE2 protein protected the mice from severe acute lung injury (p. 112, col. 2; Figures 2(d)-(f)). This study employed the ***same*** ACE2 knockout mouse model described in the present specification, the ***same*** lung elastance assay described in the specification (*see* p. 40, ln. 12-20), and a route of administration (intraperitoneal injection) ***disclosed*** in the specification (*see* p. 21, ln. 27-30). Thus, Imai *et al.* demonstrate that those of skill in the art can treat an ACE2 decreased state by administering a therapeutically effective amount of an ACE2 polypeptide (Neu Declaration, para. 7). The results of Imai *et al.* also provide additional evidence of the conserved function of ACE2 and the renin-angiotensin system by virtue of the fact that a human ACE2 protein was able to complement ACE2 function in mice (Neu Declaration, para. 7).

In another study described in the Neu Declaration, recombinant human soluble ACE2 (rhACE2) protein was studied in a piglet acute respiratory distress syndrome (ARDS) model (Neu Declaration, para. 8). The study was conducted by Alexander Löckinger and Benedikt Treml of Dr. Neu's research group, with the pharmacological evaluation being carried out by Manfred Schuster and Hans Loibner of Apeiron Biologics (Neu Declaration, para. 8). In this study, an ACE2 polypeptide, rhACE2, was administered as a central venous bolus injection at a

dose of 100 μg/kg following the last LPS bolus injection and 120 minutes from the start of the continuous LPS infusion (Neu Declaration, para. 9). Intravenous injection is a route of administration disclosed in the present specification (*see* Specification, p. 21, ln. 27-30; Neu Declaration, para. 9). The rhACE2 bolus injections were well tolerated and did not show any apparent side effects (Neu Declaration, para. 9). Treatment with rhACE2 stabilized or even decreased slightly pulmonary arterial pressure (PAP), while the control group showed a nearly 15% increase in PAP (Neu Declaration, para. 11). Systolic arterial pressure (SAP) was also measured. The control group showed an increase in SAP up to 12%, whereas after rhACE2 injection a stabilization and 5% decrease in SAP was observed (Neu Declaration, para. 11). The difference between the control and rhACE2 treatment groups was significant (Neu Declaration, para. 11).

In addition, oxygen concentration was measured in arterial and venous blood samples taken from the piglets every 30 minutes (Neu Declaration, para. 12). There was a potential stabilization observed of arterial as well as venous oxygen concentration in the group receiving rhACE2, however the data did not reach statistical significance in this study and will have to be confirmed in further experiments (Neu Declaration, para. 12). The results of this study also provide additional evidence of the conserved function of ACE2 and the renin-angiotensin system by virtue of the fact that a human ACE2 protein was used to treat pigs.

In view of the *in vivo* rat and mouse data on the role of ACE2 in cardiac, lung, and kidney diseases; the disclosed similarities of the rat, mouse, and human ACE2 sequences; and the knowledge in the art of ACE2 sequences, expression constructs, and formulations; those of ordinary skill in the art could have practiced the claimed method in a multitude of mammals

including humans. This is confirmed by the studies described in Imai *et al.* and in the Neu Declaration.

e) The Schuster Declaration

As further evidence of the enablement of the current claims, Applicants previously provided the declaration of Dr. Manfred Schuster ("Schuster Declaration"). Dr. Schuster is the Head of Research and Development at Apeiron Biologics, which is the licensee of the present patent application. The Schuster Declaration describes four studies on therapeutic uses of recombinant human soluble ACE2 (rhACE2) protein performed under Dr. Schuster's direction at Apeiron Biologics and in collaboration with researchers at University Hospital Innsbruck (Schuster Declaration, para. 2). One of these studies was directed to pulmonary hypertension in pigs, and another was directed to acute respiratory distress syndrome in pigs (Schuster Declaration, para. 2).

The Schuster Declaration states that the studies of the rhACE2 protein were pursued because of the disclosure in the present specification that ACE2 was a critical negative regulator of the renin-angiotensin system (RAS) and that the activation of ACE2 could be used to treat hypertension, cardiac disease, kidney disease, and lung disease (Schuster Declaration, para. 4). Based on teachings in the specification, a recombinant human ACE2 (rhACE2) protein was produced and provided in a physiological buffer for use in these studies (Schuster Declaration, para. 5 and 6). The recombinant human ACE2 protein used in the studies is referred to interchangeably in the Schuster Declaration as rhACE2 and APN 01 (Schuster Declaration, para. 5).

(1) Pulmonary Hypertension in Pigs

The Schuster Declaration states that by following the teachings in the present specification it was demonstrated that rhACE2 can treat pulmonary hypertension in pigs. In

particular, the Schuster Declaration (para. 13) noted teachings in the specification that: (1) ACE2 cleaves angiotensin I (Ang I) to generate Ang 1-9, and it cleaves angiotensin II (Ang II) to generate Ang 1-7 (Specification, p. 29, ln. 10-16) (*see also* Exhibit 2, Figure 1); (2) the specification discloses that ACE2 is expressed in the lung (Specification, p. 40, ln. 11-12); (3) loss of ACE2 resulted in increased sensitivity to lung injury in the ACE2 knockout mouse (Specification, p. 36, ln. 14 – p. 38, ln. 26); (4) an ACE2 decreased state, such as lung disease, may be treated by administering to an animal in need thereof an effective amount of an agent that can increase the expression of ACE2 (Specification, p. 9, ln. 10-15; p. 40, ln. 18-20); (5) the agent that can increase the expression of ACE2 can be an ACE2 protein (Specification, p. 9, ln. 16-25); and (5) the agent may be administered to a subject via intravenous injection (Specification, p. 21, ln. 27-30). Accordingly, the effects of rhACE2 administered by intravenous injection to piglets ventilated using a hypoxic gas mixture were studied (Schuster Declaration, para. 13).

The results of this study demonstrated that the treatment was well tolerated without any signs of side effects or toxicity (Schuster Declaration, para. 14). In addition, the results indicated a therapeutic benefit of administering ACE2 in pulmonary hypertension as evidenced by the significant decrease in mean pulmonary arterial pressure in animals treated with rhACE2 (Schuster Declaration, para. 14).

(2) Acute Respiratory Distress in Pigs

The Schuster Declaration also provides an update on the study previously described in the Neu Declaration. As noted in both the Schuster Declaration and the Neu Declaration, this study is a collaboration between researchers at Apeiron Biologics and University Hospital Innsbruck. The ARDS animal model provides reproducible conditions in which to evaluate the effects of administrated drugs (Schuster Declaration, para. 36). A variety of pharmacological

and physiological parameters were evaluated over the course of the study (*see* Schuster Declaration, para. 18-36). The results of the study in the ARDS piglet model demonstrate the ACE2 therapy is well tolerated and provides a therapeutic benefit (Schuster Declaration, para. 25 and 37). In particular, the study demonstrated that ACE2 therapy increased lung function and improved kidney function in the ARDS piglet model (Schuster Declaration, para. 37; *see also* para. 18-36).

Further studies in the ARDS piglet model were performed to further elucidate the mechanism behind the therapeutic effects of ACE2 treatment (Schuster Declaration, para. 49). The drug Telmisartan, which blocks AngII signaling via the AT1 receptor, was administered alone or in combination with rhACE2 to see if the therapeutic effects of the ACE2 treatment were related to reduced Ang II signaling via AT1 receptor or if other, AT1-independent effects, were responsible for the therapeutic benefit (Schuster Declaration, para. 49). The Schuster Declaration reports that the therapeutic benefit of an ACE2 therapy does not appear to be mediated only by the reduction of AT1 related signaling caused by lowered Ang II titers (para. 49).

f) The Existence of Working Examples

As mentioned above, the present invention provides working examples showing that an ACE2 decreased state is associated with cardiovascular, renal, and lung diseases (*see* Specification, p. 32, ln. 21 – p. 33, ln. 22; p. 36, ln. 8 – p. 38, ln. 12; p. 40, ln. 12-20). Specifically in regard to acute respiratory distress syndrome, ***the specification provides a working example demonstrating that ACE2 knock-out mice are more susceptible to acute respiratory distress syndrome*** (Specification, p. 39-40). Accordingly, those of ordinary skilled in the art would have understood that ACE2 plays a significant role in protecting lungs from lung injury and, therefore, would have appreciated the therapeutic benefit of treating acute respiratory

distress syndrome by administering an ACE2 polypeptide to a mammal. The specification provides the sequences of human, rat, and mouse ACE2 DNA and polypeptides (FIG. 1a, 10, and 11). The specification also discloses routes of administration and dosages at, for example, page 21, line 27 to page 22, line 17.

As described in the preceding sections, Imai *et al.* demonstrated that one skilled in the art is be able to practice the claimed invention without an undue amount of experimentation by demonstrating that a recombinant human ACE2 protein protected mice having a decreased ACE2 state from severe acute lung injury (p. 112, col. 2; Figures 2(d)-(f)) in a study that employed the same ACE2 knockout mouse model described in the present specification, the same lung elastance assay described in the specification (*see* p. 40, ln. 12-20), and a route of administration (intraperitoneal injection) disclosed in the specification (*see* p. 21, ln. 27-30) (*see also* Neu Declaration, para. 7). The enablement of the currently claimed invention is further confirmed by the study in the piglet ARDS model discussed above and described in the Neu Declaration (para. 8-12) and Schuster Declaration (para. 17-37) and in the mouse cardiovascular disease model and the mouse kidney disease model described in the Schuster Declaration at paragraphs 13-14 and 15-16.

g) Summary

In view of the animal model studies in the specification showing the role of ACE2 in cardiac, lung, and kidney diseases; the disclosed similarities of the rat, mouse, and human ACE2 structure and function; and the teaching in the specification that cardiac, lung, and kidney disease, may be treated by administering to an animal in need thereof an effective amount of an agent that can increase the expression of ACE2; a person of ordinary skill in the art could make and use the currently claimed invention without undue experimentation (*see* Neu Declaration, para. 14; *see also* Schuster Declaration, para. 51).

The enablement of the claims is confirmed by the demonstration by Imai *et al.* that injecting ACE2 knockout mice or acid-treated wild-type mice with a rhACE2 protein protected the mice from severe acute lung injury; and the study in the piglet ARDS model showing that rhACE2 protein therapy stabilized or even decreased both pulmonary arterial pressure and systolic arterial pressure (*see* Neu Declaration, para. 14). The enablement of the claims is further confirmed by the studies described in the Schuster Declaration, which demonstrate that a therapeutically effective amount an ACE2 polypeptide has a beneficial effect in treating cardiovascular complications, pulmonary hypertension, kidney disease, and acute respiratory distress syndrome.

The current claims are, therefore, enabled. Thus, Applicants respectfully request the withdrawal of this rejection.

C. *The Claims are Definite*

The Action rejects claims 67-68, 73, 100-102, 104-107, 116-120, and 125 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. These rejections are moot in view of the current claim amendments. Applicants, therefore, request the withdrawal of this rejection.

D. *The Claims Are Novel Over Acton*

Claims 67-68, 73, 100-102, 104-107, 110, 116-120, and 125 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Acton (U.S. Patent 6,194,556). Applicants traverse this rejection.

Nowhere does Acton disclose a method of treating acute respiratory distress syndrome in a mammal comprising administering a mammalian ACE2 polypeptide (or any ACE2 agonist) to the mammal. As explained on page 2 of the Specification and in multiple previous responses, Acton predicted that ACE2 functioned to hydrolyze AngI into AngII, which is a vasoconstrictor, based on its homology to ACE (Acton, col. 56, ln. 19-39). Accordingly, Acton predicted that

ACE2 ***antagonists*** would be useful in treating hypertension and congestive heart failure (Id.; *see also* col. 7, ln. 47-51; col. 57, ln. 10-20). In other words, Acton ***incorrectly predicted*** a function for ACE2 that was the ***opposite*** of it actual function. While Acton also discusses therapeutic uses of ACE2 agonists, Acton contemplated their use for the treatment of inflammation, burns, and insect bites (Acton, col. 58, ln. 7, ln. 51-54).

As mentioned in Applicants' previous response, the Examiner's mixing and matching of disparate teachings in Acton is legally flawed. *See e.g.,* 545 F.3d at 1369. Surprisingly, the Examiner responds by arguing that the legal standard for anticipation varies depending on the technology at issue (Action, p. 15). This is incorrect. Regardless of the technology, if a publication is to anticipate a claim under 35 U.S.C. § 102 it must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements arranged as in the claim. For the Examiner's convenience, here is a quote from a biotechnology-related case, which quotes the *NetMoneyIN* case that was quoted in Applicants' previous response:

> To anticipate, the reference "must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements ***'arranged as in the claim.'***" *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008) (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)); see also, e.g., *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972) ("[The] reference must clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] ***without any need for picking, choosing, and combining various disclosures*** not directly related to each other by the teachings of the cited reference."

Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075, 1083 (Fed. Cir. 2008) (brackets in original) (bold italics added).

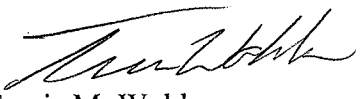
The Examiner did not identify any disclosure in Acton that even suggests using ACE2 to treat lung disease. Rather, the Examiner merely cites to disclosures in Acton of various

conditions and of various ACE2 therapeutics (ACE2 agonists or ACE2 antagonists) without any regard for which conditions Acton states could be treated with either an ACE2 agonist or antagonist. This fails to establish a *prima facie* case of anticipation, regardless of the technology at issue. Applicants, therefore, request the withdrawal of this rejection.

E. *Conclusion*

Applicants believe that this is complete reply to the Office Action dated June 1, 2009. Should the Examiner have any questions, comments, or suggestions relating to this case, the Examiner is invited to contact the undersigned Applicants' representative at (512) 536-5654.

Respectfully submitted,



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